ORIGINAL ARTICLE

Outcomes of Dolutegravir-Based Antiretroviral Therapy in Thai Youth Aged 18 to 24 Years Living with HIV in Bangkok: A Retrospective Cohort Study

Wipaporn Natalie Songtaweesin, MBBS[1,2], Chutima Saisaengjan, MA[2], Jiratchaya Soponphan, MSc[3], Patama Deeklum, BBA[2], Rachaneekorn Nadsasarn, BA[2], Lucksanapon Pitikawinwong, BSc[2], Chayapa Phasomsap, BNS[2], Thanyawee Puthanakit, MD[1,4]

[1] School of Global Health, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [2] Center of Excellence for Pediatric Infectious Diseases and Vaccines, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [3] HIV Netherlands Australia Thailand (HIV-NAT) Research Collaboration, Thai Red Cross AIDS Research Center, Bangkok, Thailand; [4] Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Objective: Dolutegravir (DTG) is recommended globally for people living with HIV. The present study aimed to describe the efficacy and safety of DTG-based regimens among youth aged 18 to 24 years.

Materials and Methods: A retrospective cohort study was conducted among youth aged 18 to 24 years living with HIV at Chulalongkorn Hospital. Participants were divided into antiretroviral naïve (AN), antiretroviral experienced with treatment failure (AETF), and antiretroviral experienced and virally suppressed (AEVS). DTG was prescribed as a daily individual tablet or as part of a fixed-dose combination. The primary outcome was virological suppression defined as VL of less than 200 copies/mL within 12 months after DTG initiation. Secondary outcomes included body weight and lipid profile changes.

Results: Between 2017 and 2022, 87 youth with a median age of 20.6 (IQR 19.6 to 21.9) years were initiated on DTG. Fifty-six (64.3%) were male. Twelve participants were AN, 18 were AETF, and 57 were AEVS. HIV viral suppression was 100% and 96.2% among those AN and AEVS respectively, but only 54.5% amongst the AETF group (p<0.001). CD4 lymphocyte counts increased in all groups at follow-up. Median body weight change was +0.4 (IQR –1.8 to 3.6) kg in males and +0.5 (IQR –2.8 to 1.7) kg in females. Median total cholesterol declined from 167 (IQR 142 to 186) to 152 (IQR 135 to 170) mg/dL, p=0.003. Median triglycerides declined from 83 (IQR 60 to 129) to 66 (IQR 46 to 78), p<0.001. No hospitalizations or mortalities were observed in the study.

Conclusion: DTG was effective and well-tolerated in youth living with HIV, with no significant weight gain and improved lipid profiles. DTG implementation among youth living with HIV should be continued.

Keywords: Dolutegravir; Antiretroviral therapy; Adolescents living with HIV

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Dolutegravir (DTG) is a second-generation integrase strand transfer inhibitor (INSTI). Its safety, tolerability and efficacy in youth has been reported in clinical studies in Thailand and internationally[1-3]. It has superior efficacy in HIV RNA viral suppression relative to non-nucleoside reverse transcriptase inhibitors (NNRTI) of 6.9%, protease inhibitors (PI) of 8.7%, and other INSTI of 8.2%, based regimens as well as greater increases in CD4 lymphocyte counts following initiation seen in a 2013-2018 meta-analysis[4]. A systematic review in 11 studies on both antiretroviral therapy (ART) naïve and experienced children and adolescents aged 0 to 19 years with a median follow-up of 6 to 36 months found viral suppression rates between 80% and 90%[5]. When compared to NNRTI- and PI-based regimens, ART naïve DTG users are more than 80% more likely to achieve and maintain plasma HIV RNA viral suppression[4].

Some youth studies have found DTG use to be associated with weight gain and improvement in lipid profiles when compared to PI- and NNRTI-based regimens[1,6,7]. Weight gain associations with DTG use is controversial in adults with studies reporting mixed results[6,8-11]. An adolescent study in Eswatini reported that in virally suppressed adolescents living

Correspondence to:

Puthanakit T.

Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, 1873 Rama IV Road, Pathumwan, Bangkok 10330, Thailand.

Phone: +66-89-6658846

Email: thanyawee.p@chula.ac.th

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with HIV switched to DTG-based regimens, body mass index (BMI) increases were notably 2.8 times higher in females[8]. Associations of DTG use and weight gain has been seen in African women and little data is available for Asian populations[12]. Switching from PI- or NNRTI- based regimens to DTG-based regimens showed a decline in total cholesterol from 201 to 160 mg/dL after the first three months, then remained stable in a study published in 2021 among Italian adolescents aged 12 to 19 years[7]. Reductions of a smaller magnitude was also seen in a systematic review comparing total cholesterol in children and adolescents receiving DTG compared to standard of care[5].

Youth living with HIV are well known to have lower drug adherence and therefore viral suppression when compared to adults due to a multitude of developmental and psychosocial factors[13-16]. In a 2014 meta-analysis on global cohorts, only 62.3% in adolescents on ART were virally suppressed[14]. Data from a Thai National Database study done in 17,825 youth aged 15 to 24 years in Thailand between 2014-2019 found that 80% achieved viral suppression at 6 to 12 months, compared to 90% in Thai adults[17,18]. Given this issue, the use of DTG, which has a high barrier to resistance and is available in Thailand should be encouraged.

The World Health Organization (WHO) has recommended DTG-based regimens as the preferred first line ART in youth since 2018[19]. Thailand's National Guidelines followed in 2021 recommending the use of DTG as a first-line ART[20]. DTG was implemented into Thailand's health services in August 2021 in the form of a single 50 mg DTG tablet and later as a fixed dose combination tablet (TLD) in May 2022. These are available to youth living with HIV under the Thai National AIDS Program in all government healthcare facilities. Given the current ongoing rollout of DTG nationally, real-world data of DTG outcomes in youth are needed to support implementation in this important key population. The primary objective of the present study was to look at rates of viral suppression and secondary outcomes were to look at change in body weight and metabolic profiles within 12 months following DTG initiation.

Materials and Methods

Study design and participants

The present study was a retrospective cohort study that looked at clinical and laboratory outcomes of youth aged 18 to 24 years living with HIV who received DTG containing regimens. Inclusion criteria were youth aged between 18 to 24 years at the time of initiating DTG between January 2017 and October 2022. Exclusion criteria were youth actively participating in other clinical trials. Follow-up data were included up to March 2023. Data was truncated at week 48.

Participants were categorized into one of three groups based upon history of ART with 1) ART naïve (AN), 2) ART experienced with treatment failure (AETF), and 3) ART experienced and virally suppressed (AEVS). The present study was conducted at 'Buddy Clinic', an adolescent HIV and STD care clinic at King Chulalongkorn Memorial Hospital, a tertiary care teaching hospital in Bangkok, Thailand. Medical ethics approval was received from the Faculty of Medicine, Chulalongkorn University Institutional Review Board (IRB No. 0508/65). The present study took place in parallel with European Pregnancy and Pediatric Infections Cohort Collaboration (EPPICC) study, a multinational study. The database collection protocol was modified from the EPPICC study protocol[21].

Procedures and outcomes

Electronic and/or paper medical records of youth included in the present study were obtained. All were assessed at baseline and followed up within 48 weeks following DTG initiation. DTG was prescribed as a 50 mg once daily individual tablet: DTG (Mylan, India), or Tegrad-50 (Hetero Labs, India), or as part of a fixed-dose combination tablet; 300 mg tenofovir disoproxil fumarate/300 mg lamivudine/50 mg DTG (TLD); Acriptega (Mylan, India).

Clinical and laboratory data were collected, including age, gender, weight, height, plasma HIV RNA, CD4 lymphocyte count, lipid profile using fasting total cholesterol and triglycerides. Body mass indices calculated were compared against Western Pacific Regional Office standards used in adults aged 18 and over in Asian populations, 18.5 to 22.9 were defined as normal range[22]. Viral suppression was defined as plasma HIV RNA of less than 200 copies/mL. Any adverse or serious adverse events while on DTG-based regimens were noted. Data on co-infections and/or co-morbidities included syphilis, hepatitis C infection and depressive symptoms. The Patient Health Questionnaire Survey (PHQ-9) translated into a validated version for use in Thai was used to screen for depressive symptoms, which was defined as scores greater than 10[23,24]. Clinical follow-up was conducted in accordance with Thai National Guidelines every three months. Annual laboratory

testing was performed and reimbursable through the Thailand's National AIDS program.

Plasma HIV RNA was detected using the Cobas 5800 assay (Roche Diagnostics) with limits of detection of less than 20 copies to 10,000,000 copies/mL. Cholesterol was measured using an enzymatic rate assay. Hypercholesterolemia was defined as a fasting serum total cholesterol level of more than 240 mg/dL, and hypertriglyceridemia of more than 200 mg/dL in accordance with the National Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) guidelines[25]. Syphilis was tested using the Elecsys® Syphilis (Roche Diagnostics, Germany) an automated electrochemiluminescence assay (ECLIA) detecting treponemal IgM and IgG antibodies, and further RPR testing for those testing positive for this. Hepatitis C was tested using the Cobas E801 analytical unit to test for anti-hepatitis C virus (HCV) using an ECLIA and HCV viral load using the Cobas 5800 system with the HCV quantitative nucleic acid test version 3.0, with limits of detection of 12 to 100,000 IU/mL.

Statistical analysis

Categorical variables were expressed as counts and percentages and continuous variables were expressed as medians and interquartile ranges (IQRs). Proportions for categorical variables were compared using chi-squared or Fisher's exact test. Continuous variables were presented as medians and compared between the three groups using the non-parametric Kruskal-Wallis test. The primary endpoint, plasma HIV RNA suppression post DTG initiation was defined as plasma HIV RNA of less than 200 copies/mL in accordance with DHHS 2023 guidelines, which were calculated in the AN and AETF groups[26]. The authors assessed the effect of DTG use on weight and lipids changes from baseline using the Wilcoxon signed-rank test. Statistical analyses were conducted using Stata Statistical Software, version 17 (StataCorp LLC, College Station, TX, USA). P-values less than 0.05 were taken to be statistically significant.

Ethical approval

The present study was approved by the Institutional Review Board of the Faculty of Medicine of Chulalongkorn University, Bangkok, Thailand (IRB No. 508/65).

Results

Baseline characteristics

Ninety-nine patients attended CU Buddy Clinic between January 2017 and October 2022 but 12 were excluded as they were on non-DTG-based regimens. The remaining 87 were included in the present study. Demographics data is shown in Table 1. The mode of HIV transmission of participants was vertical transmission in 41.3% and horizontal transmission in 58.7%. The median age at HIV diagnosis was 16.9 (IQR 7.8 to 18.9) years and median age at DTG initiation was 20.6 (IQR 19.6 to 21.9) years. Regarding gender identity, men who have sex with men (MSM) were the largest group

Table 1. Baseline characteristics of youth initiated on dolutegravir-based regimens

Characteristics	Total=87
Gender identity; n (%)	
Men who have sex with men	35 (40.2)
Transgender women	9 (10.3)
Cisgender male	12 (13.8)
Cisgender female	31 (35.7)
Route of HIV transmission; n (%)	
Vertical	36 (41.3)
Horizontal	51 (58.7)
Age (years); median (IQR)	
At time of HIV diagnosis	16.9 (7.8 to 18.9)
At dolutegravir initiation	20.6 (19.6 to 21.9)
Weight at baseline (kg); median (IQR)	54.1 (46.2 to 64.0)
Body mass index at baseline (kg/m^2); median (IQR)	19.7 (17.6 to 22.3)
ART status; n (%)	
ART naïve (AN)	12 (13.8)
ART experienced with treatment failure (AETF)	18 (20.7)
ART experienced and virally suppressed (AEVS)	57 (65.5)
Previous regimen of ART experienced participants (n=75); n (%)	
NNRTI-based	56 (74.7)
PI-based	10 (13.3)
INSTI-based	7 (9.3)
NRTTI-based	2 (2.7)
CD4 lymphocyte counts (n=74); n (%)	
Median (IQR)	534 (360 to 703)
≥500 cells/mm^3	42 (56.8)
200 to 499 cells/mm^3	25 (33.8)
<200 cells/mm^3	7 (9.4)
Co-infections or co-morbidities; n (%)	
Syphilis (n=50)	11 (22.0)
Hepatitis C (n=26)	6 (23.1)
Depressive symptoms* (n=85)	17 (20.0)

ART=antiretroviral therapy; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; INSTI=integrase strand inhibitor; NRTTI=nucleoside reverse transcriptase translocation inhibitor; IQR=interquartile range

* Depressive symptoms defined as patient health questionnaire (PHQ-9) scores ≥10

Table 2a. Baseline laboratory and weight findings of youth initiated on dolutegravir-based regimens

	All groups (n=87)	AN (n=12)	AETF (n=18)	AEVS (n=57)
Horizontal HIV transmission; n (%)	51 (58.7)	0 (0.0)	7 (38.9)	32 (56.1)
Years of HIV infection; median (IQR)	3 (1.0 to 12.8)	0 (0.0 to 0.0)	12 (3.3 to 15.0)	3 (1.0 to 12.3)
Years of antiretroviral treatment; median (IQR)	1 (0.9 to 1.5)	1 (0.6 to 1.5)	2 (1.1 to 2.4)	1 (0.9 to 1.2)
Plasma HIV RNA				
Sample available at baseline	19	3	16	NA
Baseline (log_{10} copies/mL); median (IQR)	4.1 (3.2 to 4.8)	4.6 (4.2 to 5.3)	3.9 (3.2 to 5)	NA
CD4 lymphocyte count (cells/mm^3)				
Sample available at baseline	78	7	17	54
At baseline; median (IQR)	533.5 (360 to 713)	447 (264 to 525)	301 (137 to 504)	587 (471 to 744)
Body weight (kg)				
Data available	86	12	18	56
Baseline body weight; median (IQR)	54.1 (46.2 to 64.0)	60.9 (50.4 to 65.5)	52.4 (40.0 to 60.3)	52.2 (46.9 to 64.5)
Total cholesterol (mg/dL)				
Sample available at baseline	49	N/A	8	41
Total cholesterol; median (IQR)	173 (157 to 195)	N/A	187 (140 to 203)	170 (157 to 194)
Triglycerides (mg/dL)				
Sample available at baseline	49	N/A	8	41
Triglycerides; median (IQR)	90 (66 to 126)	N/A	92 (86 to 120)	90 (65 to 129)

ART=antiretroviral therapy; AN=ART naïve; AETF=ART experienced with treatment failure; AEVS=ART experienced and virally suppressed; IQR=interquartile range; NA=not applicable, N/A=not available

at 40.2% followed by cisgender females at 35.7%. Most ART experienced participants had switched from NNRTI-based regimens at 74.7%, the remaining from PIs at 13.3%, other INSTIs (EVG, BIC) at 9.3%, and NRTTIs (Islatravir) at 2.7%. Of those tested, 22.0% and 23.1% had co-infections with syphilis and hepatitis C, respectively, and one-fifth had depressive symptoms.

Baseline laboratory and weight findings of youth are shown in Table 2a. Median baseline plasma HIV RNA was higher in the AN group when compared to the AETF group, 4.6 versus 3.9 log_{10} copies/mL, respectively. The AN group had a higher median baseline CD4 lymphocyte count than AETF group at 447 (IQR 264 to 525) cells/mm^3 versus 301 (IQR 137 to 504) cells/mm^3, respectively. Those in the AN group were all newly diagnosed with HIV and were started on DTG-based regimens on the same day or as soon as possible given social and COVID pandemic related constraints in accordance with Thai National Guidelines[20]. Participants had been diagnosed with HIV for a median for 3 (IQR 1.0 to 22.8) years and had been on ART for a median for 1 (IQR 0.9 to 1.5) year. Median years of HIV infection and ART were longest in the AETF group, at 12 (IQR 3.3 to 15) years and 2 (IQR 1.1 to 2.4) years respectively.

Efficacy in treatment

Data was collected up to March 2023. There were 72 participants who had initiated DTG for more than 48 weeks, and 15 participants with follow-up time between 23 and 47 weeks. At week 48, 70/72 (97.2%) had completed visits and 2/72 (2.7%) had been transferred out to other clinics.

There were no hospitalizations or mortalities observed during this time period. Overall, plasma HIV RNA of less than 200 copies/mL was found in 67/74 (90.5%) (95% CI 81.5 to 96.1) among those with available blood results (Table 2b). When considered separately, those AN were most successful, with 100% viral suppression, followed by 96.2% among AEFS and 54.5% among AETF group, respectively. CD4 counts across all groups increased at follow-up, a median of 336.5 to 577.5 cells/mm^3 at baseline and 463.0 to 673.0 cells/mm^3 at follow-up (Table 2b).

The two participants in the AEVS group did not achieve viral suppression at follow-up were both heterosexual vertically acquired HIV (VHIV) females ages 18 and 19 years. They were both always previously virally suppressed, one had a history of depression but had been treated and was fully recovered. One had switched from an NRTI-based regimen and the other an NRTTI-based regimen. Both

Table 2b. Baseline and follow-up comparison of laboratory and weight findings of youth initiated on dolutegravir-based regimens

	All groups	AN	AETF	AEVS
Plasma HIV RNA				
Data available after treatment	74	11	11	52
Time after DTG initiation (weeks); median (IQR)	41.1 (24.6 to 54.6)	19.6 (12.9 to 24.9)	30.9 (14.9 to 52.3)	45.0 (36.1 to 55.9)
HIV RNA <200 copies/mL; n (%)	67 (90.5)	11 (100)	6 (54.5)	50 (96.2)
CD4 lymphocyte count (cells/mm^3)				
Samples available at both baseline and follow-up	59	6	9	44
Time after DTG initiation (weeks); median (IQR)	41.6 (24.8 to 55.1)	18.7 (12.9 to 25.3)	26.0 (14.0 to 34.0)	47.0 (37.0 to 57.0)
Baseline; median (IQR)	524.0 (360.0 to 703.0)	378.5 (264.0 to 468.0)	336.5 (111.5 to 554.0)	577.5 (445.5 to 757.0)
Follow-up; median (IQR)	536.5 (435.0 to 746.0)	468.5 (336.0 to 511.0)	463.0 (120.0 to 664.0)	673.0 (505.0 to 894.0)
p-value	0.0048	0.0625	0.0801	0.0627
Body weight (kg)				
Samples available at both baseline and follow-up	79	11	16	52
Time after DTG initiation (weeks); median (IQR)	40.6 (22.9 to 54.3)	12.9 (4.1 to 22.9)	40.9 (32.4 to 51.2)	46.6 (36.0 to 57.0)
Baseline; median (IQR)	52.7 (45.0 to 63.6)	63.0 (46.6 to 66.0)	49.1 (40.6 to 54.5)	51.1 (46.3 to 63.8)
Follow-up; median (IQR)	50.0 (45.5 to 63.1)	63.0 (43.9 to 67.5)	48.9 (41.0 to 54.7)	51.0 (46.5 to 63.1)
p-value	0.4227	0.9492	0.8601	0.3405
Total Cholesterol (mg/dL)				
Samples available at both baseline and follow-up	31	N/A	4	27
Time after DTG initiation (weeks); median (IQR)	46.0 (26.9 to 56.6)	N/A	27.9 (14.0 to 46.3)	47.1 (38.9 to 57.1)
Baseline; median (IQR)	169.0 (151.0 to 194.0)	N/A	188.5 (155.0 to 202.5)	167.0 (151.0 to 187.0)
Follow-up; median (IQR)	152.5 (135 to 174)	N/A	151.0 (135.0 to 179.0)	153.0 (132.0 to 174.0)
p-value	0.0734	N/A	0.8750	0.1239
Triglycerides (mg/dL)				
Samples available at both baseline and follow-up	31	N/A	4	27
Time after DTG initiation (weeks); median (IQR)	46.0 (26.9 to 56.6)	N/A	27.9 (14.0 to 46.3)	47.1 (38.9 to 57.1)
Baseline; median (IQR)	98.0 (66.0 to 129.0)	N/A	100.5 (86.0 to 120.0)	98.0 (65.0 to 131.0)
Follow-up; median (IQR)	68.0 (50.0 to 114.0)	N/A	62.0 (56.0 to 220.0)	68.0 (50.0 to 114.5)
p-value	0.0047	N/A	0.8750	0.0046

ART=antiretroviral therapy; AN=ART naïve; AETF=ART experienced with treatment failure; AEVS=ART experienced and virally suppressed; DTG=dolutegravir; IQR=interquartile range; N/A=not available

described extremely busy work schedules leading to poor adherence at this visit, and on provision of counselling and knowledge of their viremia, both subsequently achieved viral suppression. Five participants in the AETF group that remained viremic at follow-up, who were a median age of 20 with a range of 20 to 21 years. Three had VHIV and two had horizontally acquired HIV (HHIV). Three were heterosexual females and two were transgender women. Two had switched from NNRTI-based regimens, two from PI-based regimens, and one from an EVG based regimen. The participant on the EVG-based regimen was not virally suppressed on this regimen due to poor adherence but after switching to DTG achieved viral suppression intermittently during periods of improved adherence. The five youths reported poor drug adherence for this visit, and all had a long history of poor drug adherence previously. Reasons for poor adherence in this group included mental health issues with three patients that had major depressive disorder and one that had anxiety, fear of inadvertent exposure to others, medication fatigue, fear of side effects, and dislike of services provided by hospital providing social security reimbursable care.

It is notable that those in the AETF group at baseline were noted to have the longest median years of HIV infection and years of ART compared to all groups at 12 versus 2 and 3 versus 1, respectively (Table 2a).

Weight changes and metabolic profiles

Baseline weight (IQR) was 53.4 (46.0 to 64.0) kg and BMI was 19.7 (17.6 to 22.3) kg/m² (Table 1). Weight or BMI change data when comparing baseline and follow-up values by treatment status are shown in Table 2b. Data on weight and BMI change stratified

Table 3. Weight and body mass index change in males versus females on dolutegravir-based regimens

Characteristics	Male	Female
Body weight (kg)		
Data available	56	30
Baseline weight; median (IQR)	58.5 (49.9 to 66.7)	45.0 (41.1 to 52.0)
Data available	55	27
Time after DTG initiation (weeks); median (IQR)	38.4 (22.9 to 55.9)	43.0 (13.6 to 51.6)
Last follow-up weight; median (IQR)	61.0 (50 to 68)	45.5 (38.5 to 49.1)
Difference from baseline; median (IQR)	0.4 (–1.8 to 3.6)	0.5 (–2.8 to 1.7)
p-value for difference (follow-up vs. baseline)	0.15	0.98
Body mass index (kg/m^2)		
Data available	55	29
Baseline BMI; median (IQR)	20.0 (18.3 to 22.6)	18.0 (16.7 to 22.0)
Data available	54	26
Time after DTG initiation (weeks); median (IQR)	40.3 (22.9 to 56.4)	43.0 (13.6 to 51.6)
Last follow-up BMI; median (IQR)	20.4 (17.9 to 23.1)	17.9 (16.4 to 20.4)
Different from baseline; median (IQR)	0.1 (–0.8 to 0.7)	0.1 (–1.3 to 0.5)
p-value for difference (follow-up vs. baseline)	0.47	0.87

DTG=dolutegravir; BMI=body mass index; IQR=interquartile range

p-value compared by Wilcoxon sign rank test

Table 4. Proportions of lipid abnormalities in participants on dolutegravir-based regimens as treated in patients virally suppressed at follow-up (n=51)

Characteristics	Baseline	Follow-up	p-value
Total cholesterol†	n=51	n=51	
Median (IQR)	167 (142 to 186)	152 (135 to 170)	0.003
>240 mg/dL	5 (9.8)	4 (7.8)	0.65
Triglycerides‡	n=50	n=50	
Median (IQR)	83 (60 to 129)	66 (46 to 78)	<0.001
>200 mg/dL	7 (14.0)	4 (8.0)	0.25

Wilcoxon sign-rank test and McNemar's test

Breakdown of total participants included in analysis: † Antiretroviral naïve n=5, antiretroviral experienced-treatment failure n=3, antiretroviral experienced virally suppressed n=43; ‡ Antiretroviral naïve n=5, antiretroviral experienced-treatment failure n=3, antiretroviral experienced virally suppressed n=42

by gender are shown in Table 3. Male participants had a +0.4 (IQR –1.8 to 3.6) kg in body weight, compared with +0.5 (IQR –2.8 to 1.7) kg in female participants. All AN participants had HHIV, all were male with nine MSM and three TGW.

Data analysis on lipid profile change was done in the 51 participants who achieved virological suppression, which was used as surrogate marker of good adherence. Total cholesterol and triglycerides significantly decreased at follow-up (Table 4). The median total cholesterol declined from 167 (IQR 142 to 186) to 152 (IQR 135 to 170) mg/dL (p=0.003). Median triglycerides declined from 83 (IQR 60 to 129) to 66 (IQR 46 to 78) mg/dL (p=0.001).

Discussion

The present study was a retrospective cohort study of youth aged 18 to 24 years using DTG-based regimens. It demonstrated high efficacy with high viral suppression rates of 90.5%, particularly in those AN or AEVS when switching from other regimens. It found no significant weight changes and reduced total cholesterol and triglycerides at up to 48 weeks after DTG initiation, with no hospitalizations or deaths during this period.

Efficacy of dolutegravir-based regimens

Overall viral suppression within 48 weeks in the present study was 90.5%. This compares to overall figures in other studies in youth in multiple geographic regions reporting a mix of ART naïve and ART experienced youth switching to or initiating DTG-based regimens ranging between 66% and 100%[2,3,5].

Viremic youth at baseline starting dolutegravir-based regimens

In the present study, 30 youth were viremic including 12 AN and 18 AETF, at baseline, and by their last follow-up visit at 24 to 48 weeks, 100% of AN and 54.5% AETF had achieved viral suppression. In comparison, a study in 50 French adolescents with VHIV with a median age 18.6 (IQR 14.6 to 20.2)

years, done in 2014-2015 with a similar median follow-up time of 9 (IQR 5 to 13) months, on 98% ART experienced patients who had switched from predominantly PI-based regimens, which was 70% of the cohort, 67% of those viremic at baseline achieved viral suppression at follow-up, slightly higher than seen in our study[2]. Of the 11 participants who did not achieve viral suppression at follow-up, four (36%) had never previously been virally suppressed, and the eleven declared a decrease in drug compliance. This observation has similarities to the present study where 5/7 of those who were viremic at follow-up had never been virally suppressed previously, and the seven reported poor adherence. Those in the AETF group at baseline were noted to have the longest median years of HIV infection and years of ART compared to all groups, which may have been related to medication fatigue. This is known to affect treatment adherence in children and youth living with HIV, with a study in Asian children finding those with perinatally acquired HIV were more likely to experience virological failure when older[27]. Another study in children and adolescents in Eswatini found that those on antiretroviral therapy for longer were more likely to experience virological failure[28].

Although no genotypic drug resistance testing was done in the present study, no observations of viremia in youth reporting good adherence were seen in the present study, which confers with current knowledge that DTG has a high barrier to drug resistance. Given the clear challenges youth face with drug adherence, DTG is a suitable ART choice for this key population[29].

In a previous study conducted in Thailand and the U.S. in 2011-2012, 23 adolescents with VHIV aged 12 to 17 years were all viremic at baseline and followed up for a median of 153 (IQR 55 to 193) weeks, found 83% were virally suppressed at week 4 following the switch to DTG-based regimens, but this dropped to 35% at week 144, deemed to be related to drug adherence issues with only one possibly related to emergent drug resistance[1]. This emphasizes the need for adherence support in youth living with HIV.

A study in France in 109 children and adolescents with a subgroup of 25 adolescents aged 18 to 25 years, 44% of this age group were viremic at baseline, and at a median of 24 (IQR 9 to 48) months follow-up, 72.7% of these achieved viral suppression at follow-up. All 18 to 25-year-old participants in the study were ART experienced, but in the age 5 to 17 years analyses it was noted that those ART naïve were more likely to achieve viral suppression than those viremic at baseline, which is consistent with findings in the present study[30].

Dolutegravir drug resistance

Although not collected in the present study, a clear concern with DTG use in low-middle income countries is the presence of drug-resistance genotypes in those who are naïve or treatment experienced[31]. Most data thus far are from trials using monotherapy or add-on therapy for failing regimens[32]. In the global IMPAACT P1093 study where 142 mostly highly experienced children and adolescents aged 1 to 18 years were studied on DTG and an optimized background regimen, a quarter experienced virological failure, and of these, eight, or 22%, had detectable gene resistance mutations, including five with G118R and one with R263K/R[33]. A collaborative analysis of cohort studies across Canada, Europe, and South Africa found that in 750 people with genotypic testing on DTG-based regimens, DTG resistance was rare at 0.8% high level resistance, and more likely to occur in DTG mono or dual therapy with lamivudine[34].

It is known that resistance to integrase inhibitors in ART naïve patient are rare[35]. A study in China on 1,071 adults found primary resistance to DTG in ART naïve individuals was uncommon at 0.37%, with more resistance seen in first-generation integrase inhibitors[36].

Treatment failure at follow-up

Based on the aforementioned previous study findings, in youth with viremia at baseline, the authors would expect rates of treatment failure of 17% to 34% in the first year of follow-up, which could increase up to 65%, particularly in those with VHIV based on previous figures observed in youth in U.S., Thai, and French Cohorts[1,2]. The markedly lower viral suppression rate of 54.5% in AETF in the present study compared to the 96.2% to 100% seen in AEVS and AN, respectively, points to the additional support needed in this group to achieve viral suppression in the long run, including mental health, psychosocial, and logistical support. It is notable that 5/7 of those with treatment failure at follow-up had VHIV, which is consistent with knowledge that those with VHIV are more likely to suffer from medication fatigue than their HHIV counterparts[16,37].

The question of how DTG effectiveness compares to other previously used core agents in adolescents is addressed in a systematic review and network meta-analysis in treatment naïve adults

and adolescents aged 13 years and older conducted in 2013-2019, which found that compared to other core agents such as PIs, NNRTIs, and other INSTIs, DTG was 80% more likely to achieve and maintain viral suppression when outcomes were assessed at week 96 in studies with at least 50 subjects[38]. DTG-based regimens as a favorable choice over the previously commonly used NNRTI-based regimens in young people is supported in the international study ODYSSEY, where a mix of 707 ART naïve and experienced children and adolescents from global cohorts aged 2.9 to 18 years initiating DTG-based regimens conducted in 2016-2018 found that at week 96 weeks, 47/350 versus 75/357 experienced treatment failure when comparing DTG-based and standard of care regimens respectively, with an estimated probability of 0.14 versus 0.22 (p=0.004)[39].

Virally suppressed at baseline

In the aforementioned studies in 50 French adolescents and 25 French youth aged 18 to 25 years, it was found that 17 and 14, respectively, virally suppressed adolescents at baseline maintained viral suppression at follow-up, which is consistent with the findings of the present study[2,3]. The two youths who were AEVS observed to have viremia at follow-up in this study had VHIV and had transiently poor adherence due to work commitments, emphasizing the need for continual follow-up and psychosocial support in this group also.

Weight changes on dolutegravir-based regimens

Excessive weight gain is a known concern with DTG use, particularly in ART naïve individuals, which may increase risk of cardiovascular and other metabolic diseases in the long-term[6,40,41]. There is a lack of information about the effect of DTG on weight gain in youth[8]. At a developmental stage where self-image plays a significant role in life, DTG's noted associations with weight gain in some studies, particularly in female youth, which may have adherence implications in a population already well known to struggle with ART adherence. Outcomes from some studies suggest there is evidence that INSTIs, and in particular, DTG, is associated with disproportionately excessive weight gain compared to other ART classes[1,6,7]. Weight gain in adults recorded have ranged between 1 to 4 kg, or in some studies reported as at least 10% increases in body weight[6]. Baseline median BMI in the present study was 19.7 (IQR 17.6 to 22.3) overall, which in accordance with Western Pacific Regional Office standards used in adults aged 18 and over in Asian populations is considered normal, which the range of 18.5 to 22.9[22]. In the present study during a 1-year period following DTG initiation in youth, no significant weight gains were seen.

Effect of gender and tenofovir alafenamide on weight gain

The association of weight gain with black females is well known, and its specific effects in youth was investigated in a study on the effect of DTG switch on weight in virally suppressed adolescents aged 10 to 19 years in Eswatini in 2019. It found that up to one year post DTG initiation, BMIs increased at a significantly higher rate, particularly in females with an overall of 1.2 kg/m² per year, 1.1 kg/m² in females with normal weight following DTG transition, compared to 0.3 kg/m² per year before[8]. This was not seen in gender subgroup analysis in the present study. The clear difference being the race of the present study cohort to the Eswatini study. However, data collected in Asian cohorts (Korea and Japan) between 2005 and 2020 made up of mainly young adults also point to significant weight gain associated with DTG use, particularly when combined with TAF, a known association with weight gain, while all participants in the present study were on DTG-regimens using a backbone of either TDF/FTC or TDF/3TC, which may explain observed differences[12,40,42-44].

Treatment failure and weight gain

No differences in weight change was seen when groups were stratified by ART exposure and viremia status in the present study, which is contrary to the results of a study done in DTG exposed individuals aged 13 to 62 with 14 for age younger than 19 years and a mean age of 32 years, where higher viral loads and lower CD4s were associated with obesity that emerged during treatment, possibly due to the relatively younger age group studied in the present cohort. It is known that older age is more likely to be associated with weight gain with DTG use[44]. A study done in Italy on 11 virally suppressed with VHIV adolescents aged 12 to 19 years switching from PI- or NNRTI- regimens found no significant BMI changes at 12 months post-DTG initiation, although a small study was similar to the present study's observations[7].

Timing of observable weight gain with dolutegravir-based regimens

It is possible that the follow-up period in the

present study was too short to observe any significant differences in weight changes. Although in previously observed weight gains associated with DTG use in randomized-controlled trials and observational cohort and retrospective studies on both ART experienced and naïve patients were seen as early as 24 weeks post initiation, in some studies, differences in weight gain between study arms became clearer at 96 weeks[6,40].

Lipid changes associated with dolutegravir-based regimens

INSTIs as an ART class are known to have a relatively small impact on lipid levels[43]. In those who are ART experienced, the prior regimen used before DTG switch also impacts lipid profile change. Those on PI-based regimens, that are known to be associated with hypertriglyceridemia, are more likely to see a substantial drop in total cholesterol and triglycerides following the switch to DTG-based regimens[45]. In the present study, although just ten youths had switched from PI-based regimens, significant drops between baseline and follow-up for both cholesterol and triglycerides were seen in those AEVS at follow-up, 170 to 153 mg/dL ($p=0.004$) and 99.5 to 67.0 ($p<0.001$), respectively. Although similar magnitude drops in total cholesterol and triglycerides were also seen in those AETF, this did not reach statistical significance due to the small sample size with available data. These figures are in keeping with total cholesterol measurements seen in a study of virally suppressed adolescents aged 12 to 19 years in an Italian cohort switching from PI- or NNRTI-based regimens to DTG-based regimens, which decreased from 201.5 (IQR 149 to 224) to 160.5 (IQR 124 to 191) mg/dL after the first three months, then remained stable[7].

Strengths and Limitations

The strengths of the present study were that it used real-world DTG data in a low-middle income setting in an Asian adolescent population where there is a lack of information currently to support implementation efforts. However, there were also limitations to the present study. Due to the study design being a retrospective cohort study, data collected were from clinical records and some were incomplete. The research team did take steps to check the plausibility of the data and collected data from as many sources as possible to maximize data available for analysis. In addition, the small size of the present study may have led to expected changes not detected, particularly in the AN and AEVS groups at follow-up. Only two timepoints after DTG switch conducted were analyzed in the present study with no comparisons made to data prior to DTG switch, which may have limited differences seen pre- and post-switch. No genotypic drug resistance testing was performed among participants who did not achieve HIV viral suppression. However, this was due to the history of poor antiretroviral drug adherence reported by patients who experienced treatment failure. Finally, concomitant hormonal use, which is known to be used in the studied population for either gender-affirming hormone therapy in TGW or contraception in heterosexual females, was not collected in the present study. Hormonal use is known to affect weight and lipids, effects that may have been confounding factors.

Conclusion

DTG was effective and well-tolerated in youth living with HIV. No significant weight gain was seen in youth users of DTG and significant reductions in lipids were seen after DTG initiation. DTG implementation efforts in youth living with HIV should be continued.

What is already known on this topic?

DTG is a highly efficacious first-line ART agent that has a good safety and tolerability profile for use in youth. Its use has been associated with weight gain in some studies, which could affect drug adherence in youth.

What does this study add?

No significant weight gain was seen in the Thai youth population studied with significant reduction in lipids after DTG use. DTG use in youth is associated with good clinical and safety outcomes overall, with those experiencing treatment failure at baseline requiring most adherence support.

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Conflicts of interest

The authors declare no conflict of interests.

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